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10/662,824	09/16/2003	Christian Frisch	37629-0079	2286

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EXAMINER	
PANDE, SUCHIRA	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/662,824	FRISCH ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-38 and 40-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-38, 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Arguments filed on May 30, 2008 are acknowledged. Applicant has not amended any claims. Claims 1-33 and 39 are cancelled. Currently claims 34-38, 40-45 are pending and will be examined in this action.

Response to Arguments

Re 103 rejection of claims 34-38 and 40-45 over Krebber et al.; Mersmann et al.; and Pluckthun et al.

2. Applicant's arguments filed May 30, 2008 have been fully considered but they are not persuasive.

Applicant is arguing following:

a) Examiner's analysis lacks any discussion of motivation to combine references.

b) On page 6 lines 1-4, Applicant is arguing limitations that are not recited in the instant claims.

c) Mersmann reference teaches away from the instant invention.

Examiner's response:

3. a) Examiner has used Krebber et al. as the reference that teaches

a nucleic acid molecule encoding a fusion protein comprising

aa) the first N-terminal domain of the gene III protein of filamentous phage and

ab) a (poly)peptide which is encoded by a nucleic acid sequence wherein said nucleic acid molecule does not comprise a nucleic acid sequence encoding a signal sequence for the transport of the fusion protein to the periplasm of a bacterial host cell,

The Mersmann reference has been used to teach wherein said genomic DNA fragment or expressed sequence tag (EST) is between 100 and 2000 base pairs in length and is derived from a eukaryotic organism.

Applicant argues that Examiner's analysis lacks any discussion of motivation to combine references. This is not correct because Examiner has provided the motivation to combine references which is being reproduced from last office action.

It would have been *prima facie* obvious to one of ordinary skill in the art to practice the method of Mersmann et al. (namely to fuse an antibody—polypeptide of eukaryotic origin-- to be expressed) in the method of Krebber et al. (into the vector taught by Krebber et al. at the time the invention was made. The motivation to do so is provided by Mersmann et al. who state "We describe here a direct approach to analyse phage display selected -----, based on their expression as functional scFv-pIII fusion proteins and detection via an anti-pIII monoclonal ab. Moreover, this technique cannot only be employed for detailed monitoring phage display selection but also for analyzing the antigen binding characteristics of isolated single clones. It is applicable to ***any phage display vector that couples the protein of interest to the gIII protein of M13***." (see page 52 par. 3). Thus one of ordinary skill is confident that if antibodies are fused to gIII protein the resulting fusion protein can be used to detect antigen binding. The question then arises what motivates one of ordinary skill to use a gIII protein fusion that is not displayed but instead collects in the inclusion body of the cell. Teaching of Plukthun et al. provide an insight as to what motivates one of ordinary skill to practice the method of Mersmann et al. in the method of Krebber et al. such that gIII P fusion

protein will be expressed and accumulate in the inclusion body. From the teachings of Plukthun et al. one of ordinary skill in the art knows that any successful antibody expression strategy needs to ensure that various domains of the immunoglobulins are properly stabilized with the crucial intramolecular disulphide bonds (page 216 par.1). Plukthun et al. go on to teach that there are four strategies that can be used to ensure proper folding such that these crucial thiol/disulphide bonds are formed (see page 216 par. 2-5). They state “The fourth strategy is finally to produce cytoplasmic antibodies. Antibody inclusion bodies are not fundamentally different from any other inclusion bodies and thus, may guidelines from general inclusion body production can be followed.” (see page 216 par. 5). Also see page 219 fig. 2d and Fig. legend where expression as cytoplasmic inclusion bodies with subsequent in vitro refolding is taught.

In view of the above explicit teachings of Plukthun et al. one of ordinary skill in the art has reasonable expectation of success that the antibody fused to the gIIIP N terminal construct taught by Krebber et al. will accumulate in the cytoplasm as an inclusion body due to absence of the periplasmic transport signal. Using the principles applied for purification and refolding the proteins from the inclusion bodies (see whole chapter Plukthun et al.) one of ordinary skill in the art will be able to produce a large amount of pure functional antibody using the bacterial expression system that will also be correctly folded.

b) On page 6 lines 1-4, Applicant arguing limitations that are not recited in the instant claims. The claims do not recite "---screening of antibody libraries to identify a specific binding partner (an anibody) for the fusion protein partner".

c) Examiner has not used Mersmann et al. to teach nucleic acid molecule lacks a signal sequence. The Krebber reference teaches this limitation, Mersmann et al. is used to teach that genomic DNA fragment or expressed sequence tag (EST) between 100 and 2000 base pairs in length and derived from a eukaryotic organism can be fused to gIII protein.

Therefore, Examiner finds that previously cited art is still valid and hence the rejections are being maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 34-38 and 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krebber et al. (1997) J. Mol. Biol. 268:607-618 in view of Mersmann

et al. (1998) J. of Immunological Methods 220:51-58 (provided to applicant previously) and further in view of Pluckthun et al. (1996) Producing antibodies in Escherichia coli: from PCR to fermentation. Chapter 10 pages 203-252 in Book entitled Antibody Engineering edited by John McCafferty, Hennie Hoogenboom and Dave Chiswell published by Oxford University Press.

7. Regarding claim 34, Krebber et al. teaches :

a. A nucleic acid molecule encoding a fusion protein comprising the first N-terminal domain of the gene III protein of filamentous phage and a polypeptide (See the adapter molecule shown in page 608, Fig. 1 c; and the fusions of gene III protein domains N1 and N1-N2 respectively fused to polypeptide SGCPHHHHHH (see page 610 Fig. 3d and Fig. 3d legend). The letters SGCPH represent the amino acids according to the standard single amino acid abbreviations used in the art. The figure shows the amino acid representation but the Figure 3 legend clearly describes how the nucleic acid constructs were made from starting from fd-phage fCKC construct. These nucleic acid constructs were used to express the gIIIpN1-SGCPHHHHHH and gIIIpN1-N2-SGCPHHHHHH fusions.

Krebber et al. also teach fusion of gene coding for enzyme β lactamase designated bla gene to N-terminal domain of the gene III (see page 610 fig. 3 c construct labeled N1-Bla-CT). gIIIp-N1-β lactamase gene fusion is not the preferred embodiment of the applicant's claim. Nonetheless, the construct illustrates that it is possible to create a fusion protein comprising the first N-terminal domain of the gene III protein of filamentous phage and a polypeptide encoded by a nucleic acid sequence

comprised in a genomic DNA. Instead of β lactamase gene which is of bacterial origin any other gene or EST of interest from eukaryotic organism may be fused to gIIIpN1-domain.

b. wherein said nucleic acid molecule does not comprise a nucleic acid sequence encoding a signal sequence for the transport of the fusion protein to the periplasm of a bacterial host cell. See fig. 3d and legend for fig. 3d where Krebber et al. state the gIIIp domains N1 and N1-N2 were independently expressed without signal sequence and purified. Also see page 611 par. 1.

(Note added by Examiner: Any polypeptide that is produced from the fusion to the gIIIp-N1 domain construct that lacks the nucleic acid sequence encoding a signal sequence for the transport of the fusion protein to the periplasm of a bacterial host cell—as recited in instant claim will inherently have the property that the fusion protein expressed will not be exported out to the periplasm of a bacterial host. This is because the signal sequence for export to periplasm is missing. Such a fusion protein will accumulate in the inclusion body of the bacterial cell.)

Regarding claim 35, Krebber et al. teaches a vector comprising a nucleic acid molecule according to claim 34 (See above and page 616 par. 4).

As Explained above by Examiner, when a nucleic acid sequence is cloned into the vector of claim 35 such that the fusion protein of claim 34 can be made. The resulting polypeptide upon expression will not be transported out to periplasm but will accumulate in the inclusion body as the signal required for transporting out to periplasm is purposely removed from such constructs.

Regarding claim 36, Krebber et al. teaches an expression vector (See page 616 par. 4 where cloning of fragments into vector pTFT74 under control of T7 promoter is described).

Regarding claim 37, Krebber et al. teaches bacterial host cell. These constructed vectors are transformed into E. coli host cells to make more copies of the vector (amplify the vector) itself (see page 615, par. 6) and for expression purposes the vector is transformed into a suitable host that allows high-level expression of the fusion protein (see page 616 par 4.).

Regarding claim 38, Krebber et al. teaches the host cell which is an *E. coli* cell (see page 615, par. 6 and page 616 par 4.).

Regarding claim 40, Krebber et al. teaches a method for the expression of a polypeptide/protein comprising:

a) expressing a nucleic acid molecule encoding a fusion protein in a host cell under conditions that allow the formation of inclusion bodies comprising said fusion protein, wherein

aa) the first N-terminal domain of the geneIII protein of filamentous phage, and

ab) said (polypeptide/protein. See page 616 par. 4 “The N1, N2 and N1-N2 genes (without signal sequence) were expressed in BL21 (DE3), where N1 required the presence of pLysS, and obtained as cytoplasmic inclusion bodies”.

Regarding claim 41, Krebber et al. teaches the method according to claim 40 further comprising the steps of

b) isolating said inclusion bodies; and solubilising said fusion protein. Krebber et. al. teach expression of gIIIp domain N1 protein fusions that lack signal sequence in E. coli BL21(DE3) and state these fusion proteins under consideration were obtained as cytoplasmic inclusion bodies (see page 616 par. 6). Krebber et al. go on to teach how purification was carried out and refolding of the purified fusion protein was accomplished from these inclusion bodies (see page 616, par. 6). It's inherent in the teaching that to purify the fusion protein they had to isolate the cytoplasmic inclusion bodies containing the fusion protein to purify the fusion protein. Refolding of purified protein inherently requires that the protein be in soluble form. So Krebber et al. must have isolated the inclusion bodies by using some standard technique such as centrifugation known to one skilled in the art and solubilized the inclusion bodies before they could purify and refold the gIIIp fusions. The solubilization is accomplished by treatment with a denaturing agent. Krebber et al. use 8M urea to solubilize the isolated inclusion bodies containing the fusion protein.

Regarding claim 42, Krebber et al. teaches *E. coli* host cells comprising a vector according to claim 35 (see page 615 par. 6).

Regarding claim 43, Krebber et al. teaches a host cell, *E. coli* BL21(DE3) comprising a vector according to claim 36 (see page 616 par. 4).

Regarding claims 34 and 40, Krebber et al. do not teach wherein said genomic DNA fragment or expressed sequence tag (EST) is between 100 and 2000 base pairs in length and is derived from a eukaryotic organism.

Regarding claims 44 and 45, Krebber et al. do not teach wherein said genomic DNA fragment or expressed sequence tag (EST) derived from a eukaryotic organism is 200 to 1500 base pairs long.

Regarding claims 34, 40, 44 and 45, Mersmann et al. teach wherein said genomic DNA fragment or expressed sequence tag (EST) is between 100 and 2000 base pairs in length and is derived from a eukaryotic organism (see whole article especially page 52 par. 5 section Phage display library and selection where a human (eukaryotic) library cloned into a vector pSEX81 which expresses scFv-pIII fusion protein is taught. They teach production of scFv 4.3-pIII fusion protein on page 53, par. 2 and on page 56 par. 2 they teach the sequence of the heavy and light chains of clone 4.3 have been determined and refer to Acc. No.:Y08593 for VH and Acc. No.:Y08594 for VL in EMBL database. A search for these two accession numbers in NCBI database shows Y08593 is 363 bp long while Y08594 is 324 bp long.

Thus by teaching sequence of the heavy and light chains of clone 4.3 that are 363 and 324 bp long, Mersmann et al. teach the limitation wherein said genomic DNA fragment is between 100 and 2000 base pairs in length and is derived from a eukaryotic organism---claims 34 and 40, and

by teaching sequences that at 363 and 324 bases long, Mersmann et al. teach wherein said genomic DNA fragment or expressed sequence tag (EST) derived from a eukaryotic organism is 200 to 1500 base pairs long—claims 44 and 45).

It would have been *prima facie* obvious to one of ordinary skill in the art to practice the method of Mersmann et al. (namely to fuse an antibody—polypeptide of

eukaryotic origin-- to be expressed) in the method of Krebber et al. (into the vector taught by Krebber et al. at the time the invention was made. The motivation to do so is provided by Mersmann et al. who state "We describe here a direct approach to analyse phage display selected -----, based on their expression as functional scFv-pIII fusion proteins and detection via an anti-pIII monoclonal ab. Moreover, this technique cannot only be employed for detailed monitoring phage display selection but also for analyzing the antigen binding characteristics of isolated single clones. It is applicable to ***any phage display vector that couples the protein of interest to the gIII protein of M13***." (see page 52 par. 3). Thus one of ordinary skill is confident that if antibodies are fused to gIII protein the resulting fusion protein can be used to detect antigen binding. The question then arises what motivates one of ordinary skill to use a gIII protein fusion that is not displayed but instead collects in the inclusion body of the cell.

Teaching of Plukthun et al. provide an insight as to what motivates one of ordinary skill to practice the method of Mersmann et al. in the method of Krebber et al. such that gIII P fusion protein will be expressed and accumulate in the inclusion body.

From the teachings of Plukthun et al. one of ordinary skill in the art knows that any successful antibody expression strategy needs to ensure that various domains of the immunoglobulins are properly stabilized with the crucial intramolecular disulphide bonds (page 216 par.1). Plukthun et al. go on to teach that there are four strategies that can be used to ensure proper folding such that these crucial thiol/disulphide bonds are formed (see page 216 par. 2-5). They state "The fourth strategy is finally to produce cytoplasmic antibodies. Antibody inclusion bodies are not fundamentally different from

any other inclusion bodies and thus, may guidelines from general inclusion body production can be followed." (see page 216 par. 5).

Also see page 219 fig. 2d and Fig. legend where expression as cytoplasmic inclusion bodies with subsequent in vitro refolding is taught.

In view of the above explicit teachings of Plukthun et al. one of ordinary skill in the art has reasonable expectation of success that the antibody fused to the gIIIP N terminal construct taught by Krebber et al. will accumulate in the cytoplasm as an inclusion body due to absence of the periplasmic transport signal. Using the principles applied for purification and refolding the proteins from the inclusion bodies (see whole chapter Plukthun et al.) one of ordinary skill in the art will be able to produce a large amount of pure functional antibody using the bacterial expression system that will also be correctly folded.

Conclusion

8. All claims under consideration 34-38, and 40-45 remain rejected over previously cited art.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa E Strzelecka/

Primary Examiner, Art Unit 1637

September 9, 2008